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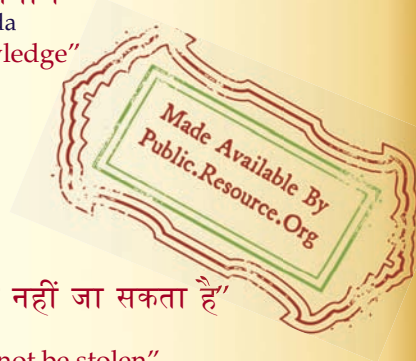
IS 12572-5 (1988): Guide for evaluation of medical devices for biological hazards, Part 5: Method of test for intracutaneous reactivity of extracts from medical devices [MHD 12: Hospital Equipment]



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“Knowledge is such a treasure which cannot be stolen”

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Indian Standard

GUIDE FOR EVALUATION OF MEDICAL DEVICES FOR BIOLOGICAL HAZARDS

PART 5 METHOD OF TEST FOR INTRACUTANEOUS REACTIVITY
OF EXTRACTS FROM MEDICAL DEVICES

भारतीय मानक

जैव-वैज्ञानिक खतरों के लिए चिकित्सीय युक्तियों के मूल्यांकन की मार्गदर्शिका

**भाग 5 चिकित्सीय युक्तियों के निष्कर्षों की अंतःत्वक प्रतिक्रियात्मकता की
परीक्षण पद्धति**

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DESCRIPTORS : MEDICAL DEVICES. BIOLOGICAL HAZARDS.
INTRACUTANEOUS REACTIVITY.

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FOREWORD

This Indian Standard (Part 5) was adopted by the Bureau of Indian Standards on 14 September 1988, after the draft finalized by the Medical Glass Instruments and Appliances Sectional Committee had been approved by the Consumer Products and Medical Instruments Division Council.

This part (part 5) is one of a series of methods of test for assessing the biological hazards of medical devices that directly come in contact with body tissues or of substances that are to be introduced in the body by means other than oral.

This standard is proposed to be published in 12 parts. Other parts are as follows:

Part 1 Terminology

Part 2 Selection of biological methods of test

Part 3 Method of testing by tissue implantation

Part 4 Method of test for systemic toxicity: Assessment of acute toxicity of extracts from medical devices

Part 6 Method of test for systemic toxicity: Assessment of pyrogenicity in rabbits of extracts from medical devices

Part 7 Methods of test for sensitization: Assessment of potential of medical devices to produce delayed contact dermatitis

Part 8 Methods of test for skin irritation of extracts from medical devices

Part 9 Method of test for skin irritation of solid medical devices

Part 10 Method of test for dental materials

Part 11 Method of test for eye irritation

Part 12 Methods of test for toxicity to cells in culture of extracts from medical devices

part 2 of this standard provides guidance On the selection of recommended methods of test for the initial assessment of biological hazards in medical devices which has been referred to in this part (Part 5) of the standard.

In the preparation of this standard, assistance has been derived from BS 5736 : Part 4 : 1981 'Evaluation of medical devices for biological hazards; Part 4 Method of' test for intracutaneous reactivity of extracts from medical devices', issued by the British Standards Institution, UK.

Indian Standard

GUIDE FOR EVALUATION OF MEDICAL DEVICES FOR BIOLOGICAL HAZARDS

PART 5 METHOD OF TEST FOR **INTRACUTANEOUS** REACTIVITY OF EXTRACTS FROM MEDICAL DEVICES

1 SCOPE

1.1 This standard describes a method of test designed to assess the **localized** reaction of tissue to **leachable** inherent or extraneous substances present in or on a medical **device**.

1.2 The method specifies use of a polar and non-polar solvent to obtain extracts that are administered as intracutaneous injections to rabbits and assessed for intracutaneous reactivity after injection at 24, 48 and 72 h thereafter.

1.3 The method of test is recommended for the initial assessment of devices in Categories A, **B₁**, C and **E₁** (see IS 12572 (Part 2) : 1988,

- a) *Category A* — Those devices intended for long-term (long-term covers a period from a few months to permanent use) implantation within the body tissue, for example, artery grafts and hip prostheses;
- b) *Category B₁* — Those devices intended for long-term (long-term covers a period from a few months to permanent use) or repeated contact with mucosal surfaces, for example, contraceptive devices;
- c) *Category C* — Those devices intended for short-term (short-term covers a period from a few minutes to several weeks continuous use) use within the body or in contact with mucosal surfaces, for example, tracheal tubes, urinary catheters and intravenous cannulae; and
- d) *Category E₁* — Those devices intended to contain or administer substances including blood, that are introduced parenterally into the body, for example, blood bags, haemodialysis equipment, intravenous administration sets and kits and hypodermic syringes.

2 DEFINITIONS

For the purpose of this standard, the following definitions shall apply.

2.1 Erythema

Tissue reaction characterized by redness at the injection site.

2.2 Eschar

Reaction characterized by scab formation.

2.3 Final Product

Medical device in its ready-for-use state.

2.4 Injection Site

The site of injection and 5 mm tissue surrounding the puncture.-

2.5 Intracutaneous Injection

Injection into the skin tissues.

2.6 Intracutaneous Reactivity

Undesirable effect(s), typically erythema or oedema which become apparent within 72 h of administration of an extract or extractant by intracutaneous injection.

2.7 Medical Device

Any item used in medical treatment, diagnosis or contraception, not intended to have a pharmacological action on the body.

2.8 Oedema

Tissue reaction characterized by swelling at the injection site.

2.9 Test Material

The final product or sample of final product that is to be tested.

3 ANIMALS AND HUSBANDRY

3.1 Four albino rabbits of a single strain, weighing not less than 2 kg each, shall be used.

3.2 The rabbits shall be housed individually and shall have free access to food and water.

4 PREPARATION OF EXTRACTS

4.1 Sterilization and Handling of Test Material

4.1.1 Test material that is pre-sterilized (refers to devices obtained sterilized from the manufacturer or supplier) shall be handled aseptically throughout the extraction and test procedure.

4.1.2 Test material that is normally supplied non-sterile but is sterilized before use, shall be sterilized before the extraction procedure and handled aseptically throughout the extraction and test procedure.

4.1.3 Test material not required to be sterilized in use shall be subjected to extraction procedure and the extracts obtained with the polar solvent shall then be sterilized before administration (see 4.2.2.1).

4.2 Extractants

4.2.1 Polar Solvent

Sterile saline solution containing 9 g/l sodium chloride.

4.2.2 Non-Polar Solvent

Sesame oil or cottonseed oil conforming to Indian Pharmacopocia.

4.2.2.1 It is recognized that it may not be practicable to sterilize the non-polar solvent. Care should be taken to minimize any possible microbiological contamination. Preparation as in 4.1.2 may be used.

4.3 Principles of Extraction

4.3.1 The test material shall be representative of the final product.

4.3.1.1 To achieve this, the test material may consist of small pieces of the final product or of one or more intact devices. For large multi-component devices (for example, dialysis units or membrane oxygenators) it may be appropriate to separately test the individual components of the device.

4.3.1.2 The quantity of any inherent or extraneous substances extracted is related to the surface of the sample (interfacial area) With which the extractant is brought into contact.

4.3.1.3 The concentration of any inherent or extraneous substances in the extract and hence the dose delivered to the test rabbit, depends on both the interfacial area and the final extract volume.

4.3.1.4 The interfacial area per unit volume of the extract has to be taken into consideration when the dose delivered to the rabbit is related to the exposure of the device to man.

4.3.2 During the extraction, the interfacial area per millilitre of final extract volume shall, where possible, be one-third of the surface area of the device that comes into direct contact either with body tissue or with mucosal surfaces and/or body fluids; or with liquids that are subsequently introduced parenterally into the body under its intended use.

NOTE --The factor of one-third arises from the consideration of the margin of safety, on the basis of an empirical dose comparison between the test animal and the man. Under the conditions given in 4.3.2, the dose per kilogram of body weight administered to the test animal is approximately one thousand times greater than that which would be received from the device under intended medical use in a man weighing 70 kg.

4.3.3 The technique used in exposing the test material to the extractant shall be selected according to the requirements of 4.3.1 and 4.3.2 and may consist of total immersion or flow-through methods, or a successive extraction of more than one specimen of the final product.

4.3.3.1 Fragmentation of the test material may be used to increase the interfacial area.

4.3.4 Extraction conditions shall simulate as nearly as possible the conditions under which the device will normally be used.

4.3.5 During the extraction, $27 \pm 3^{\circ}\text{C}$ shall be representative of the room temperature and $37 \pm 2^{\circ}\text{C}$ that of the body temperature.

4.3.6 The period of contact between the extractant and the test material shall be not less than 2 h and need not be longer than 72 h.

4.4 Procedure

4.4.1 Using the polar solvent (4.2.1) and the non-polar solvent (4.2.2) as extractants, prepare sufficient volumes of extracts of the test material in accordance with 4.1 and 4.3 to carry out the procedure described in 5.2.

4.4.2 In conditions identical with those used in 4.4.1, prepare controls using both the polar and the non-polar solvent in the absence of test material.

4.4.3 Sterilize the extracts obtained with the polar solvent from unsterilized devices (see 4.1.3).

4.4.4 Record for the test report, the precise conditions of extraction and, where applicable, of sterilization.

5 TEST PROCEDURE

5.1 Preparation of Animals

On the day before the test, clip the fur on the backs of the rabbits close to the skin to permit a sufficient distance on both sides of the spinal column for observation of all injection sites.

5.2 Administration of Extracts and Extractants

5.2.1 Inject intracutaneously 0.2 ml of the extract obtained with the polar solvent at ten sites on one side of each of the two rabbits (see Fig. 1).

5.2.2 Similarly inject 0.2 ml of the polar solvent (control) at five sites on the other side of each of the same two rabbits (see Fig. 1).

5.2.3 Repeat the procedures in 5.2.1 and 5.2.2 for the extract obtained with the non-polar solvent and the non-polar solvent (control).

5.3 Observation of Animals

5.3.1 Note the appearance of each injection site immediately after injection and at 24, 48, and 72 hours after injection.

5.3.2 Note, describe and rate the tissue reaction of erythema and oedema according to rating given in Table I for each injection site and at each time interval observed and record the results.

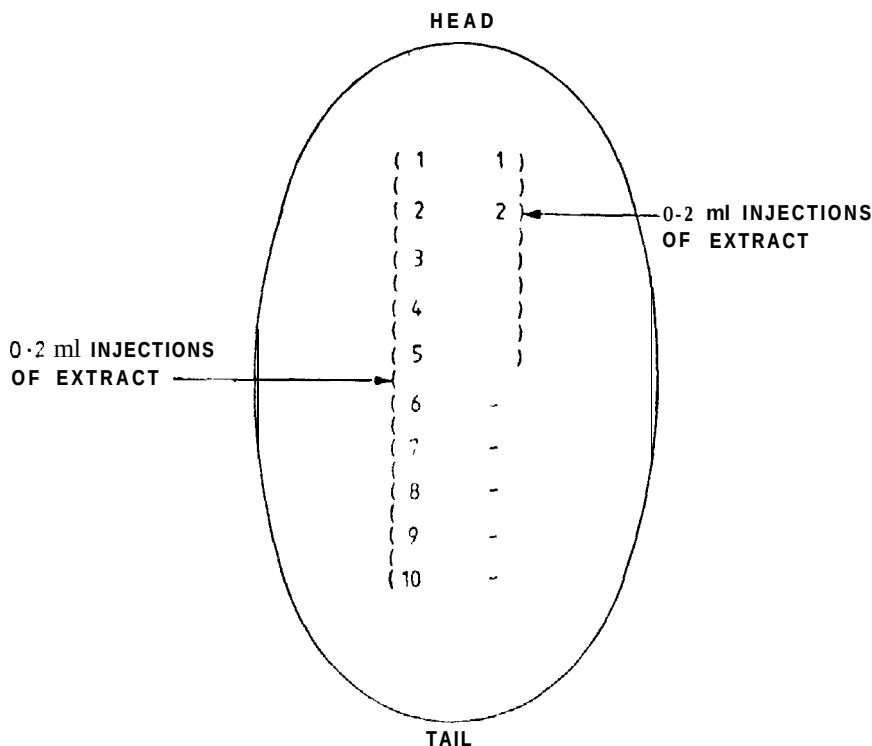


FIG. 1 ARRANGEMENT OF INJECTION SITES OF A SINGLE EXTRACT

Table 1 Rating System for Tissue Reaction
(Clause 5 3.2)

Reaction	Numerical Rating
Erythema and Eschar Formation	
No erythema	0
Very slight erythema (barely perceptible,	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (but redness) to slight eschar formation	4
Oedema Formation	
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extending beyond the area of exposure)	4

5.3.3 Determine the mean numerical rating for all observations in respect of each extract and extractant.

6 PRESENTATION OF RESULTS

The results shall be submitted in a test report that includes a complete record of the method of extraction and procedures followed, and any other relevant data necessary for the assessment of results as described in 7.

7 ASSESSMENT OF RESULTS

7.1 The assessment of the result should be carried out by an experienced person (preferably a toxicologist) who is aware of the conditions of use of the final product and has with him appropriate chemical and biological data concerning it (see 3.3 and 3.4 of IS 12572 (Part 2): 1988

7.2 The overall assessment of the test results shall be done, taking into consideration any difference observed between the mean numerical rating of an extract and the mean numerical rating of its extractant and all other information in the test report.

7.3 If the assessor (toxicologist) considers the results to be either inconclusive or invalid, the test shall be repeated using different animals, fresh extracts and if necessary, fresh extractant.

7.3.1 The non-polar solvent may produce a positive numerical rating. This need not invalidate the test.

7.4 The result of the assessment shall be recorded in the test report.

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